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<b>(21) International Application Number:</b> PCT/US92/03702 <b>(22) International Filing Date:</b> 4 May 1992 (04.05.92)  <b>(30) Priority data:</b> 705,085                      24 May 1991 (24.05.91)                      US  <b>(71) Applicant:</b> PHARMAVENE, INC. [US/US]; 35 West Watkins Mill Road, Gaithersburg, MD 20878 (US). <b>(72) Inventor:</b> BELENDIUK, George, W. ; 12 Blueberry Ridge Court, Potomac, MD 20854 (US). <b>(74) Agents:</b> OLSTEIN, Elliot, M. et al.; Carella, Byrne, Gilfilan, Cecchi & Stewart, 6 Becker Farm Road, Roseland, NJ 07068 (US).		<b>(81) Designated States:</b> AT (European patent), AU, BE (European patent), CA, CH (European patent), DE (European patent), DK (European patent), ES (European patent), FR (European patent), GB (European patent), GR (European patent), IT (European patent), JP, LU (European patent), MC (European patent), NL (European patent), SE (European patent).  <b>Published</b> <i>Without international search report and to be republished upon receipt of that report.</i>
<b>(54) Title:</b> TREATMENT OF DRUG WITHDRAWAL SYMPTOMS AND DRUG CRAVING WITH TYPE B MONOAMINE OXIDASE INHIBITORS  <b>(57) Abstract</b>  Methods of treating withdrawal symptoms and preventing or reducing craving of addictive psychostimulants (e.g., cocaine), addictive opiates, alcohol, or nicotine by administering to a patient a Type B monoamine oxidase inhibitor in an amount effective to alleviate withdrawal symptoms and prevent or reduce craving of addictive psychostimulants, addictive opiates, alcohol, or nicotine. A preferred Type B monoamine oxidase inhibitor is L-deprenyl, or selegiline.		

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**TREATMENT OF DRUG WITHDRAWAL SYMPTOMS  
AND DRUG CRAVING WITH TYPE B  
MONOAMINE OXIDASE INHIBITORS**

This invention relates to the treatment of substance abuse or addiction; in particular, to the treatment of withdrawal symptoms and to the prevention or reduction of drug craving in patients undergoing treatment for abuse of or addiction to various drugs, such as addictive psychostimulants, addictive opiates, alcohol, and nicotine. More particularly, this invention relates to the treatment of withdrawal symptoms and the prevention or reduction of drug craving through the use of Type B monoamine oxidase (MAO) inhibitors.

Cessation of the use of addictive drugs may result in a variety of undesirable physical and/or psychological symptoms. Such symptoms may include drug craving, depression, irritability, anergia, amotivation, appetite changes, nausea, shaking, psychomotoric retardation, and irregular sleep patterns, such as, for example, hypersomnia. Relief of such symptoms would aid patients in stopping the use of addicting drugs more easily and would also be useful in the post-drug recovery period.

In accordance with an aspect of the present invention, there is provided a method of treating withdrawal symptoms and preventing or reducing craving of addictive psychostimulants. The method comprises administering to a patient at least one Type B

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monoamine oxidase inhibitor (sometimes hereinafter referred to as a Type B MAO inhibitor or an MAO B inhibitor) in an amount effective to alleviate withdrawal symptoms and to prevent or reduce craving of addictive psychostimulants in a patient.

In general, such Type B monoamine oxidase inhibitors are converted by monoamine oxidase to an active moiety which combines irreversibly with the active site and/or the enzyme's essential FAD cofactor. Because such Type B MAO inhibitors have greater affinity for Type B active sites than for Type A active sites, such Type B MAO inhibitors can act as selective inhibitors of MAO Type B.

In general, a Type B MAO inhibitor may be determined by measuring MAO activity of the following samples:

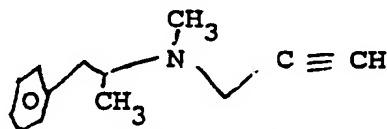
1. A biological sample (eg., a brain tissue sample or blood sample) to which no MAO inhibitors are added. (Control).
2. A biological sample to which clorgyline is added. (Clorgyline is known to be a highly selective Type A MAO inhibitor.)
3. A biological sample to which is added a substance which is being tested for selective Type B MAO inhibition.
4. A biological sample to which is added clorgyline and the substance being tested for selective Type B MAO inhibition.

Because clorgyline is a highly selective Type A MAO inhibitor, one can determine the proportion of total MAO activity which is Type A MAO activity and the proportion of MAO activity which is Type B MAO activity. If the sum of the MAO inhibitory activities of clorgyline used alone and of the substance being tested for selective Type B MAO inhibition used alone is greater than 100%, then the substance being tested for Type B MAO inhibition is not a selective inhibitor of Type B MAO. If the sum of the MAO inhibitory activities of clorgyline used alone and of the substance being tested for selective Type B MAO inhibition used alone approaches but does not exceed 100%, and the MAO inhibitory activity of a combination of clorgyline and the test

substance approaches 100%, then the test substance is a selective Type B MAO inhibitor. An example of an assay procedure for determining MAO with applications for determining Type B MAO inhibitors may be found in Belendiuk, et al., "Platelet Serotonin and Platelet MAO Activity in Individuals with Huntington's Disease," in Chase, et al., eds., Advances in Neurology, New York (1979).

In accordance with one embodiment, the at least one Type B monoamine oxidase inhibitor is selected from the group consisting of deprenyl, AGN-1135, MDL72145, and J-508. Preferably, the at least one Type B monoamine oxidase inhibitor is deprenyl.

Deprenyl exists in the forms of optical isomers; i.e., a D-isomer and an L-isomer. Most preferably, deprenyl is administered in the form of the L-isomer, also known as selegiline. Deprenyl has the following structural formula:



It is also contemplated that within the scope of the present invention selegiline may be administered in the form of selegiline hydrochloride (selegiline HCl).

AGN-1135 is further described in Youdim, et al., Adv. Neurol., Vol. 45, pgs. 127-36 (1987); MDL-72145 is further described in Fozard, et al., Naunyn Schmiedeberg's Arch. Pharmacol., Vol. 331, pgs. 186-193 (1985); and J-508 is further described in Knoll, et al., Biochem. Pharmacol., Vol. 27, pgs. 1739-1747 (1978) and Bey, et al., Br. J. Pharmacol., Vol. 81, pg. 50 (1984).

The at least one Type B monoamine oxidase inhibitor, in general, may be administered in an amount of from about 0.05 mg to about 20 mg per day, preferably from about 5.0 mg to about 10 mg per day. The at least one Type B monoamine oxidase inhibitor may be administered in a single dosage, or in multiple dosages administered at regular intervals. Alternatively, the Type B

monoamine oxidase inhibitor may be administered in accordance with a patient's individual requirements.

The at least one Type B monoamine oxidase inhibitor may be administered in free base form or in a pharmaceutically acceptable salt form. The at least one Type B monoamine oxidase inhibitor may be administered orally or parenterally. For oral administration, the at least one Type B monoamine oxidase inhibitor may be administered in a variety of forms, such as tablets, powders, granules, capsules, syrups, and elixirs. Such forms may also include acceptable pharmaceutical carriers such as diluents, granulating agents, disintegrating agents, and lubricating agents. When a tablet is employed, the tablet may be uncoated or coated by techniques known to those skilled in the art to delay disintegration and absorption in the gastrointestinal tract to provide a sustained action over an extended period. The preparation of the orally administrable forms will be apparent to those of ordinary skill in the art from the teachings contained herein.

Alternatively, the at least one Type B monoamine oxidase inhibitor may be administered parenterally, such as, for example, in the form of an aqueous injectable solution, which may be administered intramuscularly or intravenously. It is also contemplated that within the scope of the present invention that the at least one Type B monoamine oxidase inhibitor may be administered transdermally, such as for example, in a matrix adhesive patch; buccally, or intranasally by administering the at least one Type B monoamine oxidase inhibitor with conventional pharmaceutically carriers or excipients such as, for example, permeation enhancers. It is to be understood, however, that the scope of the present invention is not to be limited to any particular form of administration.

Addictive psychostimulants to which this aspect of the present invention is applicable include, but are not limited to, cocaine, amphetamines, methamphetamines, dextroamphetamines,

chlorphentermine, methylphenidate, pipradrol, p-hydroxymorphedrine, fenfluramine, 1-(2,5-di-methoxy-4-methylphenyl)-2-aminopropane (DOM), bupropion, pemoline, and analogues or derivatives thereof, such as the phosphate, sulfate, and 4-chlorophenoxy-acetate salts of amphetamines, methamphetamines, dextroamphetamines, and pemoline. Addictive psychostimulants are further described in Glennon, "Psychoactive Phenylisopropylamines," in Meltzer, ed., Psychopharmacology: The Third Generation of Progress, Raven Press, New York (1987). The present invention is particularly applicable to the treatment of patients undergoing treatment for cocaine addiction whereby the administration of at least one Type B monoamine oxidase inhibitor is employed to alleviate withdrawal symptoms associated with the cessation of cocaine use and/or prevent or reduce cocaine craving.

In accordance with another aspect of the present invention, there is provided a method of treating withdrawal symptoms and for preventing or reducing craving of addictive opiates. The method comprises administering to a patient at least one Type B monoamine oxidase inhibitor in an amount effective to alleviate withdrawal symptoms and/or prevent or reduce craving of addictive opiates in a patient. The at least one Type B monoamine oxidase inhibitor may be as hereinabove described, and may be administered in amounts hereinabove described as well.

Addictive opiates to which this aspect of the present invention is applicable include, but are not limited to, opium, including powdered opium, granulated opium, raw opium, tincture of opium, and opium fluid extracts; morphine and derivatives thereof, such as, for example, ethylmorphine; heroin and derivatives thereof.

In accordance with a further aspect of the present invention, there is provided a method of treating withdrawal symptoms and for preventing or reducing craving of alcohol by administering to a patient at least one Type B monoamine oxidase

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inhibitor, such as those hereinabove described, in an amount effective to alleviate withdrawal symptoms and prevent or reduce craving of alcohol in a patient. The at least one Type B monoamine oxidase inhibitor may be administered in amounts and in forms such as those hereinabove described.

In accordance with yet another aspect of the present invention, there is provided a method of treating withdrawal symptoms and for preventing craving of nicotine. The method comprises administering to a patient at least one Type B monoamine oxidase inhibitor in an amount effective to alleviate withdrawal symptoms and prevent or reduce craving of nicotine in a patient. The at least one Type B monoamine oxidase inhibitor may be administered in amounts and in forms such as those hereinabove described.

It is also contemplated that the methods of the present invention may be employed in conjunction with other means of treatment such as, for example, behavioral or psychological or psychiatric treatment provided by inpatient or outpatient substance abuse programs.

In a preferred embodiment, selegiline is administered in the form of a tablet containing 5 mg of selegiline hydrochloride, and the inactive ingredients lactose, starch, povidone, magnesium stearate, and talc. Such a tablet is sold under the trade name Eldepryl<sup>R</sup> by Somerset Pharmaceuticals, Inc., of Denville, New Jersey. The tablet is administered to a patient undergoing treatment for psychostimulant addiction, opiate addiction, alcohol abuse, or nicotine abuse. The tablet is administered twice daily for six weeks.

The materials and methods of the present invention may also be employed in treating withdrawal symptoms associated with and for preventing craving of addictive narcotics and of addictive barbiturates. Examples of such addictive narcotics include, but are not limited to, those commonly prescribed for pain and discomfort such as alphaprodine; anileridine; bezitramide;

codeine; dihydrocodeine; diphenoxylate; fentanyl; hydrocodone; hydromorphone; isomethadone; levomethorphan; levorphanol; metazocine; methadone; metopon; oxycodone; oxymorphone; pethidine; phenazocine; piminodine; racemethorphan; racemorphan; thebaine, or pharmaceutically acceptable salts thereof.

Examples of addictive barbiturates include, but are not limited to, allobarbital; amylbarbital; butabarbital; hexobarbital; mephobabital; methohexital; pentobarbital; phenobarbital; phenethylbarbital; secobarbital; talbutal; and thiopental.

It is to be understood, however, that the scope of the present invention is not to be limited to the specific embodiments described above. The invention may be practiced other than as particularly described and still be within the scope of the accompanying claims.

## WHAT IS CLAIMED IS:

1. A method of treating withdrawal symptoms and preventing or reducing craving of cocaine in a patient, comprising:  
administering to a patient at least one Type B monoamine oxidase inhibitor in an amount effective to alleviate withdrawal symptoms and to prevent or reduce craving of cocaine in said patient.

2. The method of Claim 1 wherein said at least one Type B monoamine oxidase inhibitor is L-deprenyl.

3. The method of Claim 1 wherein said at least one Type B monoamine oxidase inhibitor is administered in an amount of from about 0.05 mg to about 20 mg per day.

4. The method of Claim 3 wherein said at least one Type B monoamine oxidase inhibitor is administered in an amount of from about 5.0 mg to about 10 mg per day.

5. A composition for use in the method of Claim 1, comprising:

at least one Type B monoamine oxidase inhibitor and an acceptable pharmaceutical carrier, said at least one Type B monoamine oxidase inhibitor being present in an amount effective to alleviate withdrawal symptoms and prevent or reduce craving of cocaine in a patient.